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EXAMINER	
ANGELL, JON E	
ART UNIT	**PAPER NUMBER**
1635	

DATE MAILED: 03/06/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/933,115	FISHER, PAUL B.	
	Examiner	Art Unit	
	Jon Eric Angell	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 December 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *51-81* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *51-81* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *20 August 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *12/14/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This Action is in response to the communication filed on 12/14/2005.

The amendment filed 12/14/2005 is acknowledged and has been entered.

Claims 51-81 are currently pending in the application and are addressed herein.

Applicant's arguments are addressed on a per section basis. The text of those sections of Title 35, U.S. Code not included in this Action can be found in a prior Office Action. Any rejections not reiterated in this action have been withdrawn as being obviated by the amendment of the claims and/or applicant's arguments.

Information Disclosure Statement

The information disclosure statements (IDS) submitted 12/14/2005 is acknowledged. The submissions are in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement filed 12/14/2005 has been considered by the examiner.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 51-80 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant

art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to a method for inhibiting the proliferation of cancer cells having a *ras* gene mutation which increases RAS activity comprising introducing into one or more of the cells a nucleic acid, in expressible form, that is a nucleic acid that specifically hybridizes to a nucleic acid having residues 275-895 of SEQ ID NO: 1 under specific stringent hybridization conditions (e.g., see claim 51, 58, 59, 66, 73 or 80) and that encodes a protein which inhibits proliferation of melanoma cells.

"A nucleic acid that specifically hybridizes to a nucleic acid having residues 275-895 of SEQ ID NO: 1... and that encodes a protein which inhibits proliferation of melanoma cells" encompasses a genus of nucleic acids which are structurally different from a nucleic acid which encodes the polypeptide of SEQ ID NO: 2 (MDA-7), which are the only nucleic acids that would specifically hybridize to the indicated sequences of SEQ ID NO: 1 under stringent conditions and which encode a protein that inhibits proliferation of melanoma cells.

Therefore, the claims encompass a genus of nucleic acid molecules which encode variants of "MDA-7 protein" wherein the "MDA-7 protein" can be structurally different from the polypeptide disclosed as SEQ ID NO: 2. Considering that the specification clearly indicates that the invention embraces functional equivalents of the nucleic acid and protein including isolated nucleic acids which hybridize to the indicated of SEQ ID NO: 1 as set forth in the claims, the claims encompass a genus of molecules which potentially includes an enormous number of different species molecules.

It is noted that although the claims indicate that the nucleic acids encode a protein that inhibits proliferation of melanoma cells, the claims do not require that the nucleic acids possess any particular conserved structure.

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of compete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. In this case, the only distinguishing structural characteristic of the genus of molecules encompassed by the claims disclosed in the specification is that the nucleic acid hybridizes to SEQ ID NO: 1 under stringent hybridization conditions. The specification does not identify any particular portion or critical elements of the nucleic acid molecule or the encoded protein that must be conserved in order for the protein to be able to inhibit the proliferation of melanoma cells. Accordingly, the specification does not provide adequate written description of the claimed genus.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure of the encompassed genus of molecules, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of

isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

Therefore, only isolated nucleic acids encoding the amino acid sequence set forth in SEQ ID NO: 2 (which includes the nucleotide sequence that is SEQ ID NO: 1) meet the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Claims 51-81 are also rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for:

A method for inhibiting proliferation of cancer cells wherein said cancer cells comprise a mutated *ras* gene that increases *RAS* activity in the cancer cell, wherein said method comprises directly administering to said cancer cells a composition comprising:

(i) a nucleic acid that encodes and expresses the polypeptide of SEQ ID NO: 2 (MDA-7) (which includes the sequence of SEQ ID NO: 1), and

(ii) an nucleic acid molecule that specifically hybridizes under stringent conditions to a *RAS* nucleic acid molecule and that inhibits translation of *ras*-specific mRNA;

does not reasonably provide enablement for the full scope of the claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988).

Wands states on page 1404,
"Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention

The instant claims are drawn to methods of inhibiting proliferation in a population of cancer cells by administering therapeutic nucleic acid sequences. Therefore the nature of the claims is cancer gene therapy, including antisense therapy.

It is noted that the invention is in a class of invention which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Fed. Cir. 2001).

The breadth of the claims

As mentioned above, the claims are very broad. The claims encompass methods of "treating" cancer (including inhibiting proliferation in a population of cancer cells) by increasing the amount of MDA-7 protein via introduction of a nucleic acid molecule which encodes MDA-7 into a cancer cell, and decreasing the activity of *RAS* in said cancer cell by introducing a nucleic

acid molecule that hybridizes under stringent conditions to a *RAS* nucleic acid molecule and inhibits translation of *ras*-specific mRNA (e.g., an antisense-*ras* oligonucleotide).

It is noted that the claims do not indicate that the nucleic acids are administered by any particular route of administration; therefore, the claims encompass any route of administration, including general systemic administration of the nucleic acid molecules.

It is also noted the broad claims encompass to a method for inhibiting proliferation in a population of cancer cells having a *ras* gene mutation which increases *RAS* activity. As such, these claims encompass any type of cancer that has any *ras* gene mutation which increases *RAS* activity in the cancer cell.

The specification does not provide an enabling disclosure for the full scope of the claims for the following reasons: (1) the claims encompass any route of administration, including systemic delivery of the nucleic acid molecules, (2) the claims encompass administering nucleic acids which encode variants of SEQ ID NO: 2 which are capable of inhibiting proliferation of melanoma cells without providing sufficient guidance to indicate to one of skill in the art which variants would encode a polypeptide that has the desired function and which variants would have the required function.

The unpredictability of the art and the state of the prior art

The claims encompass methods of inhibiting the proliferation of cancer cells and treating cancer by administering nucleic acid molecules to a subject having the cancer cells wherein the nucleic acids are administered by any route of administration including systemic delivery.

However, at the time of invention, the relevant art recognizes several problems associated with the general systemic administration of nucleic acids to subjects for treating cancer.

For instance, it is well established in the art that delivery is one of the key problems of gene therapy. Anderson (Nature 1998; 392(suppl):25-30, previously cited) teaches,

> "The challenge is to develop gene therapy as an efficient and safe drug delivery system. The goal is more difficult to achieve than many investigators had predicted... The human body has spent many thousands of years learning to protect itself from the onslaught of environmental hazards, including the incorporation of foreign DNA into its genome. (See p. 25, second paragraph). The ultimate goal of gene therapy research is the development of vectors that can be injected, will target specific cells, will result in safe and efficient gene transfer into a high percentage of those cells, will insert themselves into appropriate regions of the genome (or will persist as stable episomes), will be regulated be either by administered agents or by the body's own physiological signals, will be cost effective and will cure disease." (See p. 30, first paragraph).

Crystal (Science 1995; 270:404-410; previously cited) also indicates some of the problems regarding gene therapy in general. Specifically, regarding the obstacles of human gene transfer, Crystal teaches, "The [gene transfer] vector (should) be specific for its target, not recognized by the immune system..." (See p. 409, column 2 under "The perfect vector").

Finally, regarding the delivery of gene therapy vectors to tumors, Greco (Frontiers in Biosci. 2002; 7:d1516-1524; previously cited) teaches,

> "The administration of gene therapy vectors requires that they be not only targeted, but also protected from degradation, sequestration or immune attack, in order to reach the appropriate sites for transfection. Although some success has been reported for naked DNA, efficient delivery has been restricted to intratumoral injection." (See p. 1517, paragraph bridging columns 1-2).

Indicating that direct delivery of the therapeutic nucleic acid to the desired site of transfection is critical for delivering the nucleic acid to the appropriate cells.

Therefore, the art, at the time of filing, indicates that administration of nucleic acid molecules by systemic administration is an inefficient, and thus unpredictable, means of administering therapeutic nucleic acid molecules to specific target cells in a subject.

As noted above, the claims encompass methods comprising administering nucleic acid molecules which encode structural variants of SEQ ID NO: 2 (but which are functionally the same). There is no indication in specification or prior art which indicates that any nucleic acid sequence other than a nucleic acid sequence encoding SEQ ID NO: 2 inhibits proliferation of melanoma cells, nor is there any guidance indicating any critical structures of the polypeptides encompassed by the claims which must be present in order for the polypeptides to have the desired function (inhibition of proliferation of melanoma cells). The specification merely identifies the variants by indicating variants include nucleic acid sequences that hybridize to SEQ ID NO: 1 under stringent hybridization conditions (e.g., see page 18 of the specification). Therefore, the variants encompassed by the claims include nucleic acid sequences that encode polypeptide that have a different amino acid sequence than the MDA-7 polypeptide of SEQ ID NO: 2.

The prior art teaches that changing a single amino acid can completely change the function of a polypeptide. For instance, Witkowski et al. (Biochemistry 38:11643-11650, 1999) teaches that one amino acid substitution transforms a β-ketoacyl synthase into a malonyl decarboxylase and completely eliminates β-ketoacyl synthase activity. Seffernick et al. (J. Bacteriol. 183(8):2405-2410, 2001) teaches that two naturally occurring Pseudomonas enzymes having 98% amino acid sequence identity catalyze two different reactions: deamination and dehalogenation, therefore having different function. Additionally, the genus of nucleic acid molecules has the potential of encompassing a coding sequence that comprises a stop codon that would prematurely terminate translation of the encoded polypeptide possibly resulting in a non-functional peptide fragment. Therefore, without sufficient guidance, one of skill in the art would

not be able to identify which sequences encompassed by the claims would encode a protein that inhibits proliferation of melanoma cells and which ones would not without performing additional experimentation. Considering the enormous number of different variant sequences encompassed by the claims which must be tested in order to determine which encode proteins having the required function and which ones do not, the amount of additional experimentation required to practice the claimed invention to its full scope is undue.

Working Examples and Guidance in the Specification

The specification discloses working examples that indicate the administration of a combination of an adenoviral vector that encodes and expresses SEQ ID NO: 2 (MDA-7) and an antisense nucleic acid that specifically hybridizes to a nucleic acid encoding a mutant *ras* mRNA, synergistically inhibited the growth of human pancreatic carcinoma cells having a Ki-ras mutation that results in increased RAS activity in the cells when the composition was directly administered to these specific cancer cells (e.g., see Figures 5 and 6). The effect was seen only in pancreatic cancer cells that had a mutant K-*ras* gene (not in any other pancreatic cancer cell line). The effect of the combination treatment on pancreatic cancer cells is synergistic because the effect of the combination is greater than the sum of both treatments individually (See Figures 5-6). Several different antisense molecules were tested, including antisense molecules that specifically hybridized to K-ras as well as "scrambled" and "mismatched" antisense sequences; however, only the antisense molecules specific for mutant K-ras mRNA demonstrated the anti-cancer effect. The anti-cancer effect of the combination was demonstrated in cancer cell lines (in vitro) as well as in tumors in mice (wherein the composition was administered directly to the tumors).

Level of the skill in the art

The level of the skill in the art is deemed to be high.

Quantity of Experimentation

Considering the breadth of the claims, an additional experimentation would have to be performed in order for one of skill in the art to be able to practice the invention to the full scope encompassed by the claims. For instance, additional experimentation would be required with respect to the genus of nucleic acid molecules encoding the protein encompassed by the claims, but not adequately described. Further experimentation would be required to overcome the art-recognized problems associated with systemic administration of nucleic acids for cancer therapy. Considering the problems recognized in the art at the time of filing with respect to systemic administration of nucleic acid molecules and the enormous number of different nucleic acid molecules which encode MDA-7 protein encompassed by the claims, it is clear that the additional experimentation required to practice broadly claimed invention to its full scope is not routine. Therefore the amount of additional experimentation required is deemed to be undue.

Conclusion

Considering the breadth of the claims, the unpredictable nature of the invention as recognized in the prior art, the limited working examples and guidance in the specification, and the high degree of skill required, it is concluded that the amount of experimentation required to perform the broadly claimed invention to its full scope is undue.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 51, 54-56, 58, 59, 62-64 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 2 and 5-17 of U.S. Patent No. 5,710,137 in view of Saison-Behmoaras et al. (EMBO J., 1991; 10(5):1111-1118).

The instant claims are drawn to a method for inhibiting proliferation in a population of cancer cells having a *ras* gene mutation which increases *RAS* activity comprising administering a nucleic acid sequence which encodes a protein which inhibits the proliferation of melanoma cells (e.g., SEQ ID NO: 2, which is MDA-7) and a nucleic acid molecule that hybridizes under

stringent conditions to a *RAS* nucleic acid molecule and inhibits translation of *ras*-specific mRNA.

It is noted that the claims encompass inhibiting proliferation in a population of any cancerous cells having the indicated *ras* gene mutation (such as cancerous cells having a Ha-*ras* mutation) as well as administering a nucleic acid molecule that hybridizes under stringent conditions to a *RAS* nucleic acid molecule and inhibits translation of *ras*-specific mRNA (such as an antisense-*ras* oligonucleotide).

An obvious-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examined application claim is not patently distinct from the reference claims(s) because the examined claims are either anticipated by, or would have been obvious over, the reference claim(s). See e.g., *In re Berg,* 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman,* 11 F.3d1046, 29 USPQ2d 2010 (Fed. Cir.) 1993).

Here claims 1, 2 and 5-17 of U.S. Patent No. 5,710,137 are drawn to a method comprising introducing a nucleic acid molecule comprising an MDA-7 gene or gene product into a cancer cell (claims 1 and 9), wherein the cancer cell is in a subject and the nucleic acid molecule is introduced into the cancerous cell (claims 2 and 10), wherein the cancerous cell is characterized by presence of a dominant acting oncogene (claims 5), wherein the dominant acting oncogene is Ha-ras (i.e., a mutant *ras* gene that increases *RAS* activity) (claims 6), wherein the nucleic acid is comprised in a vector (claim 7), wherein the vector is an adenovirus vector, adenoassociated virus vector, a retrovirus or a vaccine virus vector (claim 8), wherein the cancer cell is a breast, cervical, colon, prostate, nasopharyngeal, lung, connective tissue, or

nervous system cell (claim 11), as well as pharmaceutical a composition comprising said nucleic acid comprising an MDA-7 gene (claims 12-16).

The indicated claims of U.S. Patent No. 5,710,137 differ from the instant claims the examined application in that the claims of U.S. Patent No. 5,710,137 fail to disclose that the method further comprises a nucleic acid molecule that hybridizes under stringent conditions to a *RAS* nucleic acid molecule and inhibits translation of *ras*-specific mRNA (such as an antisense-*ras* oligonucleotide).

However, Saison-Behmoaras et al. teaches that an antisense-*ras* oligonucleotide which hybridizes to a *RAS* nucleic acid molecule and inhibits translation of *ras*-specific mRNA (specifically and antisense-Ha-*ras* oligonucleotide that inhibits translation of Ha-*ras* mRNA) can be used to inhibit the proliferation of cells having a mutant Ha-*ras* gene (i.e., an oncogenic Ha-ras gene) (e.g., see p. 1111, abstract; p. 1116, first column of text and Figure 6; etc.).

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art to modify the indicated claims of U.S. Patent No. 5,710,137 such that the method further comprised administering an antisense-ras oligonucleotide that inhibits translation of the oncogenic Ha-ras mRNA with a reasonable expectation of success.

One of skill in the art would have been motivated to combine the references to create claimed invention because the claims of U.S. Patent No. 5,710,137 and the method taught by Saison-Behmoaras are equivalent methods that that inhibit the proliferation of cancer cells having a oncogenic Ha-ras gene that increases RAS activity (e.g., see Figure 1 of U.S. Patent 5,710,137 as well as Figure 6 of Saison-Behmoaras).

MPEP 2144.06, in discussing art recognized equivalence for the same purpose, mentions *In re Kerkhoven*, wherein the court expressed the following:

"It is *prima facie* obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose...[T]he idea of combining them flows logically from their having been individually taught in the prior art." *In re Kerkhoven* 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980).

Claims 51-53, 57, 59-61 and 65 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 2 and 5-17 of U.S. Patent No. 5,710,137 in view of Saison-Behmoaras et al. (EMBO J., 1991; 10(5):1111-1118) and further in view of WO 97/16547 A1 (Roth et al.).

The instant claims are drawn to a method for inhibiting proliferation in a population of cancer cells having a *ras* gene mutation which increases *RAS* activity comprising administering a nucleic acid sequence which encodes MDA-7 protein and a nucleic acid molecule that hybridizes under stringent conditions to a *RAS* nucleic acid molecule and inhibits translation of *ras*-specific mRNA, wherein the nucleic acid molecule that hybridizes under stringent conditions to a *RAS* nucleic acid molecule is comprised in a viral vector, and wherein the viral vector further comprises a nucleic acid encoding MDA-7 in expressible form.

It is noted that the claims encompass inhibiting proliferation in a population of any cancerous cells having the indicated *ras* gene mutation (such as cancerous cells having a Ha-*ras* mutation) as well as administering a nucleic acid molecule that hybridizes under stringent

conditions to a *RAS* nucleic acid molecule and inhibits translation of *ras*-specific mRNA (such as an antisense-*ras* oligonucleotide).

An obvious-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examined application claim is not patently distinct from the reference claims(s) because the examined claims are either anticipated by, or would have been obvious over, the reference claim(s). See e.g., *In re Berg,* 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman,* 11 F.3d1046, 29 USPQ2d 2010 (Fed. Cir.) 1993).

Here claims 1, 2 and 5-17 of U.S. Patent No. 5,710,137 are drawn to a method comprising introducing a nucleic acid molecule comprising an MDA-7 gene or gene product into a cancer cell (claims 1 and 9), wherein the cancer cell is in a subject and the nucleic acid molecule is introduced into the cancerous cell (claims 2 and 10), wherein the cancerous cell is characterized by presence of a dominant acting oncogene (claims 5), wherein the dominant acting oncogene is Ha-ras (i.e., a mutant *ras* gene that increases *RAS* activity) (claims 6), wherein the nucleic acid is comprised in a vector (claim 7), wherein the vector is an adenovirus vector, adenoassociated virus vector, a retrovirus or a vaccine virus vector (claim 8), wherein the cancer cell is a breast, cervical, colon, prostate, nasopharyngeal, lung, connective tissue, or nervous system cell (claim 11), as well as pharmaceutical a composition comprising said nucleic acid comprising an MDA-7 gene (claims 12-16).

The indicated claims of U.S. Patent No. 5,710,137 differ from the instant claims the examined application in that the claims of U.S. Patent No. 5,710,137 fail to disclose that the method further comprises a nucleic acid molecule that hybridizes under stringent conditions to a *RAS* nucleic acid molecule and inhibits translation of *ras*-specific mRNA (such as an antisense-

ras oligonucleotide) or that the method can comprise administering a viral vector comprising a nucleic acid sequence encoding MDA-7 in expressible for as well as a nucleic acid that expresses a nucleic acid that inhibits the translation of a *ras*-specific mRNA.

Saison-Behmoaras et al. teaches that an antisense-*ras* oligonucleotide which hybridizes to a *RAS* nucleic acid molecule and inhibits translation of *ras*-specific mRNA (specifically and antisense-Ha-*ras* oligonucleotide that inhibits translation of Ha-*ras* mRNA) can be used to inhibit the proliferation of cells having a mutant Ha-*ras* gene (i.e., an oncogenic Ha-ras gene) (e.g., see p. 1111, abstract; p. 1116, first column of text and Figure 6; etc.). Saison-Behmoaras et al. does not teach that the antisense oligonucleotide can be delivered using an adenoviral vector.

Additionally, WO 97/16547 A1 (Roth et al.) teaches the use of an adenoviral vector to deliver and express an antisense oligonucleotide in a cancer cell. Specifically, Roth teaches an adenoviral vector that expresses an antisense-K-ras oligonucleotide wherein the vector can be used to deliver and express the antisense oligonucleotide in a cancer cell (e.g., see abstract; page 4, lines 6-16; the paragraph bridging pages 4-5; Examples 3 and 4, pages 53-55; etc.). Furthermore, Roth explicitly teaches antisense therapy in combination with other gene therapies and indicates that the combination therapy may produce an improved anticancer treatment (see page 44 lines 14-24). Roth also teaches that the expression vector will be an efficient method for delivering a therapeutically effective gene to counteract clinical disease (see page 43, lines 25-29).

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art to modify the indicated claims of U.S. Patent No. 5,710,137 such that the method further comprised administering an antisense-ras oligonucleotide that inhibits translation of the oncogenic Ha-ras

mRNA, wherein the antisense-ras oligonucleotide as well as the nucleic acid encoding the MDA-7 protein are delivered to the cancer cells using an adenoviral vector that encodes and expresses both the antisense-ras oligonucleotide and the MDA-7 protein, with a reasonable expectation of success.

One of skill in the art would have been motivated to combine the references to create claimed invention because (1) the claims of U.S. Patent No. 5,710,137 and the method taught by Saison-Behmoaras are equivalent methods that that inhibit the proliferation of cancer cells having a oncogenic Ha-ras gene that increases RAS activity (e.g., see Figure 1 of U.S. Patent 5,710,137 as well as Figure 6 of Saison-Behmoaras); and (2) Roth teaches that antisense therapy can be used in combination with other therapies including gene therapy and indicates that the viral vector encoding the antisense nucleic acid can further comprise and express other genes of interest (e.g., see page 33, lines 28-31; page 34, lines 2-4; page 39, lines 5-11; and page 44, lines 14-24).

MPEP 2144.06, in discussing art recognized equivalence for the same purpose, mentions *In re Kerkhoven*, wherein the court expressed the following:

"It is *prima facie* obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose...[T]he idea of combining them flows logically from their having been individually taught in the prior art." *In re Kerkhoven* 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 51, 54-56, 58, 59, 62-64 are rejected under 35 U.S.C. 103(a) as being obvious over U.S. Patent No. 5,710,137 in view of Saison-Behmoaras et al. (EMBO J., 1991; 10(5):1111-1118).

The applied reference (U.S. Patent No. 5,710,137) has a common inventor with the instant application. Based upon the publication date of the patent, it constitutes prior art under 35 U.S.C. 102(b). Therefore, this rejection under 35 U.S.C. 103(a) is not subject to exclusion/disqualification under 35 USC 103(c) See MPEP § 706.02(l)(1) and § 706.02(l)(2).

The instant claims are drawn to a method for inhibiting proliferation in a population of cancer cells having a *ras* gene mutation which increases *RAS* activity comprising administering a nucleic acid sequence which encodes MDA-7 protein and a nucleic acid molecule that hybridizes under stringent conditions to a *RAS* nucleic acid molecule and inhibits translation of *ras*-specific mRNA.

It is noted that the claims encompass inhibiting proliferation in a population of any cancerous cells having the indicated *ras* gene mutation (such as cancerous cells having a Ha-*ras* mutation) as well as administering a nucleic acid molecule that hybridizes under stringent conditions to a *RAS* nucleic acid molecule and inhibits translation of *ras*-specific mRNA (such as an antisense-*ras* oligonucleotide).

U.S. Patent No. 5,710,137 teaches a method comprising introducing a nucleic acid molecule comprising an MDA-7 gene or gene product into a cancer cell (claims 1 and 9), wherein the cancer cell is in a subject and the nucleic acid molecule is introduced into the cancerous cell (claims 2 and 10), wherein the cancerous cell is characterized by presence of a dominant acting oncogene (claims 5), wherein the dominant acting oncogene is Ha-ras (i.e., a mutant *ras* gene that increases *RAS* activity) (claims 6), wherein the nucleic acid is comprised in a vector (claim 7), wherein the vector is an adenovirus vector, adenoassociated virus vector, a retrovirus or a vaccine virus vector (claim 8), wherein the cancer cell is a breast, cervical, colon, prostate, nasopharyngeal, lung, connective tissue, or nervous system cell (claim 11), as well as pharmaceutical a composition comprising said nucleic acid comprising an MDA-7 gene (claims 12-16).

U.S. Patent No. 5,710,137 does not teach that that the method further comprises a nucleic acid molecule that hybridizes under stringent conditions to a *RAS* nucleic acid molecule and inhibits translation of *ras*-specific mRNA (such as an antisense-*ras* oligonucleotide).

However, Saison-Behmoaras et al. teaches that an antisense-*ras* oligonucleotide which hybridizes to a *RAS* nucleic acid molecule and inhibits translation of *ras*-specific mRNA (specifically and antisense-Ha-*ras* oligonucleotide that inhibits translation of Ha-*ras* mRNA) can be used to inhibit the proliferation of cells having a mutant Ha-*ras* gene (i.e., an oncogenic Ha-ras gene) (e.g., see p. 1111, abstract; p. 1116, first column of text and Figure 6; etc.).

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time of filing to modify the method taught by U.S. Patent No. 5,710,137 such that the method further comprised administering an antisense-ras oligonucleotide that inhibits translation of the

oncogenic Ha-ras mRNA (as taught by Saison-Behmoaras) with a reasonable expectation of success.

One of skill in the art would have been motivated to combine the references to create claimed invention because the method taught by U.S. Patent No. 5,710,137 and the method taught by Saison-Behmoaras are equivalent methods that that inhibit the proliferation of cancer cells having a oncogenic Ha-ras gene that increases RAS activity (e.g., see Figure 1 of U.S. Patent 5,710,137, as well as Figure 6 of Saison-Behmoaras).

MPEP 2144.06, in discussing art recognized equivalence for the same purpose, mentions *In re Kerkhoven*, wherein the court expressed the following:

"It is *prima facie* obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose...[T]he idea of combining them flows logically from their having been individually taught in the prior art." *In re Kerkhoven* 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980).

Claims 51-53, 57, 59-61 and 65 are rejected under 35 U.S.C. 103(a) as being obvious over U.S. Patent No. 5,710,137 in view of Saison-Behmoaras et al. (EMBO J., 1991; 10(5):1111-1118) and further in view of WO 97/16547 A1 (Roth et al.).

The applied reference (U.S. Patent No. 5,710,137) has a common inventor with the instant application. Based upon the publication date of the patent, it constitutes prior art under 35 U.S.C. 102(b). Therefore, this rejection under 35 U.S.C. 103(a) is not subject to exclusion/disqualification under 35 USC 103(c) See MPEP § 706.02(l)(1) and § 706.02(l)(2).

The instant claims are drawn to a method for inhibiting proliferation in a population of cancer cells having a *ras* gene mutation which increases *RAS* activity comprising administering a nucleic acid sequence which encodes MDA-7 protein and a nucleic acid molecule that hybridizes under stringent conditions to a *RAS* nucleic acid molecule and inhibits translation of *ras*-specific mRNA.

It is noted that the claims encompass inhibiting proliferation in a population of any cancerous cells having the indicated *ras* gene mutation (such as cancerous cells having a Ha-*ras* mutation) as well as administering a nucleic acid molecule that hybridizes under stringent conditions to a *RAS* nucleic acid molecule and inhibits translation of *ras*-specific mRNA (such as an antisense-*ras* oligonucleotide).

U.S. Patent No. 5,710,137 teaches a method comprising introducing a nucleic acid molecule comprising an MDA-7 gene or gene product into a cancer cell (claims 1 and 9), wherein the cancer cell is in a subject and the nucleic acid molecule is introduced into the cancerous cell (claims 2 and 10), wherein the cancerous cell is characterized by presence of a dominant acting oncogene (claims 5), wherein the dominant acting oncogene is Ha-ras (i.e., a mutant *ras* gene that increases *RAS* activity) (claims 6), wherein the nucleic acid is comprised in a vector (claim 7), wherein the vector is an adenovirus vector, adenoassociated virus vector, a retrovirus or a vaccine virus vector (claim 8), wherein the cancer cell is a breast, cervical, colon, prostate, nasopharyngeal, lung, connective tissue, or nervous system cell (claim 11), as well as pharmaceutical a composition comprising said nucleic acid comprising an MDA-7 gene (claims 12-16).

U.S. Patent No. 5,710,137 does not teach that that the method further comprises a nucleic acid molecule that hybridizes under stringent conditions to a *RAS* nucleic acid molecule and inhibits translation of *ras*-specific mRNA (such as an antisense-*ras* oligonucleotide).

Saison-Behmoaras et al. teaches that an antisense-*ras* oligonucleotide which hybridizes to a *RAS* nucleic acid molecule and inhibits translation of *ras*-specific mRNA (specifically and antisense-Ha-*ras* oligonucleotide that inhibits translation of Ha-*ras* mRNA) can be used to inhibit the proliferation of cells having a mutant Ha-*ras* gene (i.e., an oncogenic Ha-ras gene) (e.g., see p. 1111, abstract; p. 1116, first column of text and Figure 6; etc.). Saison-Behmoaras et al. does not teach that the antisense oligonucleotide can be delivered using an adenoviral vector.

Additionally, WO 97/16547 A1 (Roth et al.) teaches the use of an adenoviral vector to deliver and express an antisense oligonucleotide in a cancer cell. Specifically, Roth teaches an adenoviral vector that expresses an antisense-K-ras oligonucleotide wherein the vector can be used to deliver and express the antisense oligonucleotide in a cancer cell (e.g., see abstract; page 4, lines 6-16; the paragraph bridging pages 4-5; Examples 3 and 4, pages 53-55; etc.). Furthermore, Roth explicitly teaches antisense therapy in combination with other gene therapies and indicates that the combination therapy may produce an improved anticancer treatment (see page 44 lines 14-24). Roth also teaches that the expression vector will be an efficient method for delivering a therapeutically effective gene to counteract clinical disease (see page 43, lines 25-29).

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art to modify the method taught by U.S. Patent No. 5,710,137 such that the method further comprised administering an antisense-ras oligonucleotide that inhibits translation of the oncogenic Ha-ras

mRNA, wherein the antisense-ras oligonucleotide as well as the nucleic acid encoding the MDA-7 protein are delivered to the cancer cells using an adenoviral vector that encodes and expresses both the antisense-ras oligonucleotide and the MDA-7 protein, with a reasonable expectation of success.

One of skill in the art would have been motivated to combine the references to create claimed invention because (1) the method taught by U.S. Patent No. 5,710,137 and the method taught by Saison-Behmoaras are equivalent methods that inhibit the proliferation of cancer cells having a oncogenic Ha-ras gene that increases RAS activity (e.g., see Figure 1 of U.S. Patent 5,710,137 as well as Figure 6 of Saison-Behmoaras); and (2) Roth teaches that antisense therapy can be used in combination with other therapies including gene therapy and indicates that the viral vector encoding the antisense nucleic acid can further comprise and express other genes of interest (e.g., see page 33, lines 28-31; page 34, lines 2-4; page 39, lines 5-11; and page 44, lines 14-24).

MPEP 2144.06, in discussing art recognized equivalence for the same purpose, mentions *In re Kerkhoven*, wherein the court expressed the following:

"It is *prima facie* obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose...[T]he idea of combining them flows logically from their having been individually taught in the prior art." *In re Kerkhoven* 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980).

Response to Arguments

Applicant's arguments filed 12/14/2005 have been fully considered by the Examiner.

With respect to the rejection of claims under 35 USC 112, 1st paragraph (Written Description) Applicants argue that the instant claims have remedy the objections presented by the Examiner because the claim provides a detailed description of the function and properties of the hybridizing nucleic acid sequence.

This is not persuasive because the claims encompass nucleic acids which encode structural variants of MDA-7 which have the same function as MDA-7 but the specification and prior art of record do not provide a sufficient description of the structural features of MDA-7 protein which are critical for is ability to inhibit the proliferation of melanoma cells. As such, there is an insufficient description of the nucleic acids encompassed by step (i)(c) of the instant base claims. It is noted that there is a sufficient description for any nucleic acid which encodes SEQ ID NO: 2 (MDA-7) and limiting the claims as such would overcome this rejection.

With respect to the rejection of claims under 35 USC 112, 1st paragraph (scope of enablement) Applicants argue that the instant claims overcome the objections ii-iv previously set forth by the Examiner.

This is note persuasive with respect to objection ii because objection ii indicated that the claims were not fully enabled because the claims encompassed a large genus of molecules which would have to be tested in order to determine which variants of SEQ ID NO: 2 encompassed by the claims would be functional and which would not. It is acknowledged that the instant claims have added the limitation that the variant protein must be able to inhibit the proliferation of melanoma cells, having considering the lack of knowledge with respect to the structure-function

relationship of the proteins encompassed by the claims (as indicated above), further experimentation is still required in order to determine which variants would have the required function and which would not.

With respect to objection (i) set forth by the Examiner (not enabled for any route of administration other than direct delivery to the cancer cells), Applicants have submitted three articles as evidence of enablement: (1) Boulikas, (2) Shi and Pardridge, and (3) Heish et al. These references have been considered by the Examiner but are not persuasive to overcome the instant rejection. Boulikas is not sufficient to overcome the instant rejection because it teaches the intravenous administration of liposome comprising cisplatin, which is not a therapeutic nucleic acid sequence. It is noted that Boulikas describes its invention as "a method for encapsulating cisplatin or other positively charged drugs into liposomes..." (see abstract). Therefore Boulikas is not applicable to the instant case because nucleic acids are not positively charged molecules. Furthermore, the instant claims are not limited to using the liposome described by Boulikas by intravenous administration. The claims encompass any route of administration (including oral administration) of any nucleic acid encompassed by the claims (including naked DNA, plasmids, viral vectors, etc.). The Shi reference is not persuasive because it merely teaches that a nucleic acid encoding a gene of interest can be delivered to the brain by intravenous administration of a neutral pegylated immunoliposomes (e.g., see abstract). Shi does not teach that the nucleic acid was able to specifically target cancer cells. It is also respectfully pointed out that the instant claims limited to using the immunoliposome described by Shi by intravenous administration. The claims encompass any route of administration (including oral administration). Pardridge teaches a specific cytotoxic adenovirus that can be

systemically administered and selective replicate in tumor cells wherein the tumor cells in which the adenovirus replicates in lyse as a result of the adenoviral replication. The teaching of Pardridge is not relevant because the adenoviral vector taught by Pardridge is not a gene therapy vector, per se, because it does not rely on the expression of a therapeutic nucleic acid (such as a gene or antisense nucleic acid) in the tumor cell to kill the cell, as is the case in the instant application. Furthermore, the instant claims are not limited to using the ONYX-015 adenovirus to deliver the therapeutic nucleic acids which must be expressed in the tumor cells.

The instant claims encompass administering any nucleic acid that encodes and expresses the therapeutic nucleic acids (e.g., plasmids) by any route of administration (e.g., oral administration, etc.) and the cited references do not provide an enabling disclosure for the entire breadth of the claims. It is noted that limiting the claims to delivering a nucleic acid which encodes and expresses MDA-7 polypeptide (SEQ ID NO: 2) by direct delivery to the target tumor cells would obviate this rejection.

Conclusion

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after

the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jon Eric Angell whose telephone number is 571-272-0756. The examiner can normally be reached on Mon-Fri, with every other Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on 571-272-0811. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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ANNE-MARIE FALK, PH.D
PRIMARY EXAMINER